Serotonin receptor activity profiles (5-HT$_{2B}$ and 5-HT$_{2A}$) for nine commercialized ergot alkaloids correspond to known risks of fibrosis and hallucinations

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OBJECTIVE

To test the commonly described link between 1) 5-HT$_{2B}$ and 5-HT$_{2A}$ stimulation and 2) risks of fibrosis and hallucinations, respectively, by examining the receptor activity and safety profiles of nine commercialized ergot alkaloids.

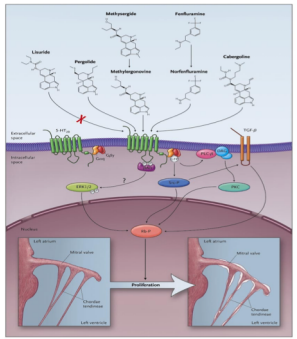
BACKGROUND

The universal skeleton of the ergot alkaloids – the 4-ring ergoline nucleus – contains the essential structural elements found in the neurotransmitters dopamine, serotonin, and epinephrine. As a result, the marketed ergot alkaloids behave as non-selective pharmacological agents with a propensity to interact with numerous neurotransmitter receptors. Some such interactions are necessary for a compound to have particular desired pharmacological effects, but others may be associated with undesirable side effects.

Receptor activities at two serotonin receptors, 5-HT$_{2B}$ and 5-HT$_{2A}$, are of specific interest due to their close association with specific adverse events. Compounds that are potent, full agonists at the 5-HT$_{2B}$ receptor have been linked to a risk of retroperitoneal, pleural or cardiac valvular fibrosis (Figure).[1-9] Potent, full agonists at the 5-HT$_{2A}$ receptor pose a risk of psychotic side effects such as hallucinations.[10-12]

Using novel receptor behavior mapping techniques, we generated 5-HT$_{2B}$ and 5-HT$_{2A}$ neuroreceptor activity profiles for nine historically marketed ergot alkaloid compounds. The profiles were evaluated against the known fibrotic- and psychotic-effect liabilities of the compounds.

Marketed 5-HT$_{2B}$ Agonists and Valvular Heart Disease



From Roth BL. Drugs and valvular heart disease. N Engl J Med. 2007 Jan 4;356(1):6-9.[5]

PLC-β = phospholipase C-β; PKC = protein kinase C; DAG = diacylglycerol; ERK = extracellular regulated kinases; TGF-β = transforming growth factor β; βArr = β-arrestin; Rb-P = retinoblastoma protein

METHODS

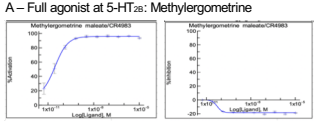
Nine ergot alkaloids were tested on 5-HT$_{2B}$ and 5-HT$_{2A}$ human recombinant G protein-coupled receptors using a CHO-K1-mt aequorin Gα16 cell line and IP-One assays (Euroscreen Laboratory, Belgium).

Dose-response curves for the nine test compounds were generated over the concentration range of 0.01 to 20,000 nM to determine effective concentration (EC$_{50}$), inhibitory concentration (IC$_{50}$) and relative degree of agonistic and antagonistic response ("relative response"). Relative responses were then compared to literature-based ratings of the risks of fibrosis and hallucinations.

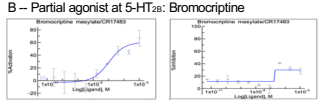
RESULTS

Dose-response Curves for Activity of Methylergometrine (Full Agonist), Bromocriptine (Partial Agonist) and Terguride (Antagonist) at the 5-HT$_{2B}$ Receptor

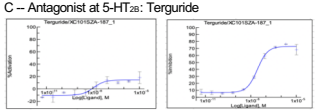
A – Full agonist at 5-HT$_{2B}$: Methylergometrine



B – Partial agonist at 5-HT$_{2B}$: Bromocriptine



C – Antagonist at 5-HT$_{2B}$: Terguride



5-HT$_{2B}$ Receptor Activity for Nine Ergot Alkaloids

	EC$_{50}$ (nM)	IC$_{50}$ (nM)	Relative Response[b]	Fibrotic effects
Methylergometrine[a]	0.2	None	Full agonist	Yes[1,4,5,7]
Cabergoline	0.6	None	Full agonist	Yes[1,3,4,5]
Pergolide	0.7	None	Full agonist	Yes[1,3,4,5]
Ergotamine	5.3	None	Full agonist	Yes[1,3,4,7]
Dihydroergotamine	52	None	Full agonist	Possible[1,4]
2-Bromocriptine	100	None	Partial agonist	Unlikely[3,4,8,9]
Lisuride	2.0	None	Partial agonist	No[4,5,6]
Methysergide	1.5	1.6	Silent antagonist[c]	No[d][3,4,5,7]
Terguride	None	27	Antagonist	No[2,4]

[a] Methylergometrine = methylergonovine (principal metabolite of methysergide)
[b] Relative response is based on the % activation or % inhibition relative to a reference standard; By % activation: full agonist >80; partial agonist 20-80; no activity <20; antagonist = % inhibition ≥20.
[c] Silent antagonists block a receptor and prevent other agents from docking, but do not necessarily display any intrinsic receptor activity.
[d] Methysergide treatment is associated with fibrotic risk due to activity of its metabolite, methylergometrine.[5]

5-HT$_{2A}$ Receptor Activity for Nine Ergot Alkaloids

	EC$_{50}$ (nM)	Relative Response	Hallucinations[10-12]
Methylergometrine[a]	0.02	Full agonist	Yes
Lisuride	0.3	Full agonist	Yes
Pergolide	0.3	Full agonist	Yes
2-Bromocriptine	0.8	Full agonist	Yes
Ergotamine	0.9	Full agonist	Yes
Cabergoline	1.2	Full agonist	Yes
Terguride	2.5	Full agonist	Yes
Methysergide	5.1	Full agonist	Yes
Dihydroergotamine	19	Full agonist	Yes

[a] Methylergometrine = methylergonovine (principal metabolite of methysergide)

DISCUSSION

- This is the first published mapping of 5-HT$_{2B}$ and 5-HT$_{2A}$ neuroreceptor activity of these 9 major ergot alkaloids based on the human recombinant G protein-coupled receptors using the CHO-K1-mt aequorin Ga16 cell line.
- The ranking of the test compounds by relative response at the 5-HT$_{2B}$ receptor is consistent with their ranking by risk of fibrosis, a major liability of some of these compounds. The full agonists pose a significant risk of fibrosis. At the other end of the activity scale, the two compounds with antagonist activity – terguride and methysergide – are not, themselves, considered to pose a risk of fibrosis.
- These data support a direct link between 5-HT$_{2B}$ activation and fibrosis. The difference in relative response between methysergide and its metabolite, methylergometrine, supports prior reports indicating it is the metabolite that accounts for the risk of fibrotic effects.[5]
- All of the compounds were shown to be full agonists at the 5-HT$_{2A}$ receptor, in line with their clinical history of posing a risk of hallucinations, although that risk can be less for compounds with higher EC$_{50}$ values.

CONCLUSIONS

- The agreement between activity at the 5-HT$_{2B}$ receptor and the risk of fibrotic effects supports the reported causal link between use of the marketed ergot alkaloids and fibrosis.
- The full-agonist behavior of all 9 tested ergot alkaloids at the 5-HT$_{2A}$ receptor is consistent with their known risk of causing hallucinations and other psychotic effects.
- Novel ergot compounds, free of agonism at the 5-HT$_{2B}$ and 5-HT$_{2A}$ receptors, may confer substantial safety advantages over existing compounds in patients with migraine, Parkinson's disease and other ergot-responsive conditions.

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